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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/005,318	01/09/98	HEIN M	310098401C1

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EXAMINER	
ROMEO, D	
ART UNIT	**PAPER NUMBER**
1646	11

DATE MAILED: 03/09/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/005,318	Hein et al.
Examiner	**Group Art Unit**
David S. Romeo	1646

☒ Responsive to communication(s) filed on *13 Dec 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-31 and 36-41* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-31 and 36-41* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-31 and 36-41* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of group I, claims 1-31, 36-41, in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants' traversal is moot in view of cancellation of the non-elected claims.

2. Applicant's election with traverse of SEQ ID NO:1, peptide bond, and gentamicin in Paper Nos. 8 and 10 is acknowledged. The traversal is on the ground(s) that there is no basis for limiting the claims to a specific sequence, biological agent, or linking means. This is not found persuasive because a teaching, motivation, and suggestion to make each of the specific sequences, biological agents, or linking means and/or a teaching, motivation, and suggestion to make each of the multifactorial combinations thereof requires separate searches in areas where pertinent art to either one or the other does not exist, thus requiring non-coextensive searches. However, some of the species may be rejoined if allowable subject matter can be agreed upon.

The requirement is still deemed proper and is therefore made FINAL.

3. Claim 6 is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, 37 C.F.R. § 1.822(e), which states in part "A sequence that is made up of one or

more noncontiguous segments of a larger sequence or segments from different sequences shall be presented as a separate sequence."

Correction is required.

4. The application is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See Tables III-XI. This list is not meant to be exhaustive.

Correction is required.

Claim Rejections - 35 USC § 112

5. Claims 1-31, 36-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a targeting molecule (TM) linked to a biological agent, wherein said TM comprises a native J chain, does not reasonably provide enablement for a TM linked to a biological agent, wherein said TM comprises a polypeptide that forms (a) and contains (b), for variants that differ only in conservative amino acid substitutions and/or modifications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are no functional limitations to the TMs that are not limited to a native J chain. The claims encompass all essentially all TMs targeting all conceivable targets. The specification

teaches targeting of the pIgR with a native J chain. The specification does not provide guidance for targeting all conceivable targets with TMs that are structurally unrelated to a native J chain. In the absence of this information the skilled artisan is left to extensive random mutational analysis of over 100 amino acid residues before they could rationally design a TM that targets a molecule other than a pIgR or that functions in a manner instantly disclosed. Furthermore, there is a lack of predictability in the art. See Bowie et al. (W_{11}) page 1306, column 1, full paragraph 1, wherein it is taught that predicting structure, hence function, from primary amino acid sequence data is extremely complex, and it unlikely the problem will be solved in the near future. Ngo et al. (X_{11}) teach that the native structure of a protein is a unique three-dimensional structure into which the protein folds under physiological conditions and all the information necessary to determine the native structure can be contained in the primary amino acid sequence (page 433, full paragraph 1). However, it is not even known whether there exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone (page 492, full paragraph 2).

A single means claim, i.e., where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. In re Hyatt , 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor.). When claims depend on a recited property, a fact situation

comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor.

The limitations "conservative substitution and/or modification variants", "binding agent", "inhibitors", and "targeting molecule" are analogous to a single means claim of the type disparaged by the court. The problem with these limitations is that they cover every conceivable means which achieves the desired activity, whereas the specification discloses at most only those means known to the inventor. As such, the limitations encompass compounds that are structurally unrelated to those instantly disclosed. The specification fails to teach the skilled artisan how to make such structurally unrelated compounds that have the desired activity or will perform in the manner instantly disclosed. Furthermore, the instant specification does not identify those structural features of a "binding agent", "inhibitor", or "targeting molecule" which are essential for the desired activity those which are not. In the absence of this information a practitioner would have to resort to a substantial amount of unduly extensive experimentation in the form of random analysis of all compounds before they could even begin to rationally make a "binding agent", "inhibitor", or "targeting molecule" other than those instantly disclosed.

The specification has not told the skilled artisan how to non-covalently link a biological agent directly to a J chain. In the absence of this information a practitioner would have to resort to a substantial amount of unduly extensive random, trial and error experimentation in order to

achieve the claimed invention. Such extensive, random, trial and error experimentation is considered undue.

Claims 7-9, 11, 20-28 encompass a polypeptide comprising a nucleotide sequence. The specification has not told the skilled artisan how to make a polypeptide comprising a nucleotide sequence.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and use the full scope of the claimed invention.

6. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19-28 are indefinite over the recitation of "a sequence recited in" because it is unclear if the sequence or some porion thereof "recited in" is intended. The metes and bounds of the claim(s) are not clearly set forth.

Claim(s) 30, 40 are indefinite because they recite the terms "binding agent" and "inhibitor". Because the instant specification does not identify that material element or combination of

elements which is unique to, and, therefore, definitive of either a "binding agent" or an "inhibitor" an artisan cannot determine what additional limitations are placed upon a claim by the presence of these terms.

Claims 6, 11, 13, 16, 18 are indefinite because they recite a Markush group in an improper Markush format. The metes and bounds of the Markush group are not clearly set forth. When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper. See M.P.E.P. 2173.05(h).

Claims 6, 7, 8, 9, 11, 13, 16, 18 are indefinite over the recitation of "conservative substitutions and/or modifications" because it is unclear if the "modifications" are conservative or are some other type of modification. The metes and bounds of the claim(s) are not clearly set forth.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim(s) 1, 2, 6-18, 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferkol et al. (AM, cited by Applicants). Ferkol et al. teach a targeting molecule (TM) linked to a biological agent. The specification defines conservative substitutions as any substitution or modification that results in a variant that retains binding specificity. The TM consists of a portion or variant of a J chain that differs only in conservative amino acid substitutions such that the TM binds to an epithelial basolateral factor.

9. Claims 1-3, 6-18, 31, 36, 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Lemaitre-Coelho et al. (ZZ11). Lemaitre-Coelho et al. teach a polymeric Fcα of human monoclonal IgA that binds rat FSC and is actively transferred into bile (page 262, column 2, full paragraph 1; paragraph bridging pages 263-264). The polymeric Fcα of human monoclonal IgA contains the human J chain and J chains are highly conserved. The polymeric Fcα of human monoclonal IgA is a targeting molecule (TM) that comprises the instantly disclosed human J chain or a portion or variant thereof, and binds to an epithelial basolateral factor. There are limited to no structural or functional limitations to the biological agent, binding agent, or inhibitor. The polymeric Fcα of human monoclonal IgA comprises a protein, a binding agent, and inhibitor, a reactive combining site, amino acids, or a drug that affects the renal system albeit negatively.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-31, 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over [[Terskikh et al. (AN, cited by Applicants) and Ferkol et al. (AM, cited by Applicants)] in view of [Morton et al. (VV11), Carayannopoulos et al. (Z_{11}) and Carayannopoulos et al. (UU_{11})]], and further in view of [Weissleder et al. (V_{11}), Janoff et al. (A11), Shen et al. (B11), Weiner et al. (C11), Pierce Chemical Company Catalog (Y_{11})].

Terskikh teaches that CEA is one of the best markers for in vivo tumor targeting of radiolabeled antibodies and teaches a recombinant dimeric IgA that translocates efficiently across a monolayer of epithelial cells expressing the pIgR and to retain full CEA binding activity (Abstract); the results suggest that the antibody will be a useful tool for targeting carcinomas in patients (page 1318, column 2, full paragraph 2).

Ferkol teaches that the pIgR is specifically adapted for the internalization of large molecules including IgA and that this receptor is an ideal candidate for receptor mediated gene transfer (page 2394, column 2, full paragraph 2). Ferkol's anti-SC agent provides greater

specificity for the targeted cells than the natural ligand IgA, which can bind to alternative receptors, such as Fc receptors, on other cell types (paragraph bridging pages 2397 and 2399).

Terskikh and Ferkol do not teach a targeting molecule (TM) linked to a biological agent (BA) wherein the TM is not a full length dimeric IgA.

Morton teaches the recombinant expression of human IgA (Materials and Methods).

Carayannopoulos (Z11) teaches the recombinant expression of human IgA (Materials and Methods).

Carayannopoulos et al. (UU11) teaches the localization of the Fc receptor binding site on IgA (Abstract; paragraph bridging pages 1583-1584).

Morton, Carayannopoulos et al. (Z11), and Carayannopoulos et al. (UU11) do not teach a TM linked to a BA wherein the TM is not a full length dimeric IgA.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a TM linked to a BA that binds to the pIgR wherein the TM is a full length dimeric IgA, as taught by Terskikh and Ferkol, and to modify that teaching by deleting or mutating the Fc receptor binding site on IgA, as taught by Morton, Carayannopoulos et al. (Z11), and Carayannopoulos et al. (UU11), with a reasonable expectation of success. One of ordinary skill in the art would be motivated to delete or mutate the Fc receptor binding site because this would provide greater specificity of the TM for the targeted cells by preventing the binding of the

TM to alternative receptors, such as Fc receptors, on other cell types. Such a deleted or mutated TM is not a full length dimeric IgA.

[Terskikh and Ferkol] in view of [Morton, Carayannopoulos et al. (Z11), and Carayannopoulos et al. (UU11)] teach a TM linked to a BA wherein the TM is not a full length dimeric IgA. [Terskikh and Ferkol] in view of [Morton, Carayannopoulos et al. (Z11), and Carayannopoulos et al. (UU11)] do not teach a TM linked to a BA wherein the TM is not a full length dimeric IgA wherein the TM is linked via a covalent bond to gentamicin.

Weissleder teaches an implantable gentamicin conjugate; gentamicin was chosen because of its free amino group and prior use in aminoglycoside conjugation (page 839, paragraph bridging columns 1-2).

Janoff teaches: "2.1. THE AMINOGLYCOSIDE ANTIBIOTICS. The aminoglycoside antibiotics (e.g., streptomycin, gentamycin, kanamycin, tobramycin, etc.) are used almost exclusively to treat infections caused by bacteria. Their mode of bactericidal action involves inhibition of protein synthesis in susceptible microorganisms. Some susceptible microorganisms include Escherichia spp., Haemophilus spp., Listeria spp., Pseudomonas spp., Nocardia spp., Yersinia spp., Klebsiella spp., Enterobacter spp., Salmonella spp., Staphyloccocus spp., Streptococcus spp., Mycobacteria spp., Shigella spp., and Serratia spp., to name but a few. The antibiotics in the aminoglycoside group all contain amino sugars in glycosidic linkages. They are polycations and their polarity is primarily responsible for the pharmacokinetic properties shared by

the members of the group. For instance, these drugs are not adequately absorbed after oral administration, they do no easily penetrate the cerebrospinal fluid, and they are rapidly excreted by the kidney. Serious toxicity is a major limitation to the usefulness of aminoglycosides. Three types of toxicity are often encountered with the use of aminoglycosides: (1) ototoxicity, which can involve both auditory and vestibular functions of the eighth cranial nerve; (2) nephrotoxicity, which is manifest as acute tubular damage; and (3) acute toxicity, which can follow intrapleural and intraperitoneal administration and is manifest as a neuromuscular blockade culminating in respiratory distress." (column 2, lines 25-53).

Shen teaches: "One potentially promising route to achieve selective delivery of a drug or protein across epithelial or endothelial cells is to use receptors as markers and receptor-building ligands as vehicles for their transcellular transport [Rodman, J. S., Mercer, R. W. and Stahl, P. D. (1989) Current Opinion in Cell Biology 2, 664-672]. This type of carrier-mediated transport is known as receptor-mediated transcytosis, which has been demonstrated in epithelial and endothelial cells for the transport of hormones [King, G. L. and Johnson, S. M. (1985) Science 227, 1583-1586], albumin [Ghitescu, L., Fixman, A., Simionescu, M. and Simionescu, N. (1986) J. Cell Biol. 102, 1304-1311], and immunoglobulins [Rodewald, R. (1980) J. Cell Biol. 85, 18-32; Underdown, B. J. (1989) Immunol. Invest. 18, 287-297]. Drug delivery via receptor-mediated transcytosis is highly specific because it enhances only the transport of molecules that are conjugated to receptor-binding ligands. In addition, drug delivery via transcytosis is also specific

for receptor-bearing cells, and therefore, a targeted delivery system can be developed [Gregoriadis, G., Poste, G., Senior, J. and Trouet, A. (eds.), Receptor-Mediated Targeting of Drugs, Plenum Press, New York (1984)]." (column 8, lines 25-47).

Weiner teaches: "This invention relates to methods and compositions which are used to enhance retention of administered bioactive agents at specific tissue or organ sites in the body of man or animals. The present invention involves covalent linkage of fibronectin to bioactive agents or their carriers to form conjugates having high affinity for collagen-, heparin-, fibrin/fibrinogen-, hyaluronic acid-, or ganglioside-rich body sites. Methods and compositions described herein have a wide range of applicability to the field of drug delivery systems. The practice of the present invention is demonstrated herein by way of example for the localized delivery of medicament to joints by intra-articular administration of the medicament entrapped in liposomes with enhanced affinity for joints conferred by fibronectin covalently cross-linked to the lipid bilayer (column 1, lines 10-18); and, "Factor XIII is utilized in the present invention to catalyze the crosslinking of fibronectin to a number of substrates. Presumably the crosslinking occurs via an acyl transfer reaction in which the γ-carboxamide group(s) of peptide-bound glutamyl residue(s) of fibronectin function as acyl donors. Substrates containing a plurality of amines function as acyl acceptors. These substrates include but are not limited to: lipids, such as phosphatidylethanolamine, phosphatidylserine, etc. which are incorporated into liposome membranes; proteins such as fibrinogen, etc.; peptide hormones such as somatotropin or growth hormone, luteinizing hormone,

etc.; aminoglycosides such as gentamicin, neomycin, tobramycin, and kanamycin, etc. Thus, fibronectin may be conjugated directly to a lipid molecule which is incorporated into a liposome or to a bioactive agent. It should be noted that the transglutaminase catalyzed reaction is carried out in an aqueous buffer; therefore, lipid substrates (which are not soluble in aqueous solutions) must be incorporated into liposomes in order to function as the enzyme substrate in the aqueous reaction mixture (column 5, lines 4-25).

Pierce Chemical Company Catalog teaches linking a targeting molecule to a biological agent (page E-8) and linkers for achieving same (pages E-15, E-21, E-58). In using any of the linkers the biological agent would linked to the targeting molecule via a peptide bond.

Weissleder, Janoff, Shen, Weiner, and Pierce Chemical Company Catalog do not teach a TM linked to a BA wherein the TM is not a full length dimeric IgA wherein the TM is linked via a covalent bond to gentamicin. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a TM linked to a BA wherein the TM is not a full length dimeric IgA, as taught by [Terskikh and Ferkol] in view of [Morton, Carayannopoulos et al. (Z11), and Carayannopoulos et al. (UU11)], and to modify that teaching by covalently linking via a peptide bond gentamicin to the not a full length dimeric IgA, as taught by Weissleder, Janoff, Shen, Weiner, Pierce Chemical Company Catalog, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because gentamicin is used to treat infections caused by bacteria, and covalently linking gentamicin to the TM would

selectively delivery the gentamicin across epithelial cells using the pIgR, and thereby avoiding serious toxicity which is a major limitation to the usefulness of gentamicin. The J chain of such a TM is a conservative substitution and/or modification variant of those instantly disclosed and/or claimed. The J chain of such a TM comprises a sequence recited in any one of the sequences instantly disclosed and/or claimed because the phrase "a sequence recited in" has been interpreted to mean a single amino acid. The invention is prima facie obvious over the prior art.

Double Patenting

12. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

13. Claims 1-31, 36-41 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims of copending Application No. 08782481. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-31, 36-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 08782481. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications appear to be claiming the same types of targeting molecules (TM). The TMs of the instant invention are generic to and encompass the TMs of the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-31, 36-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Applications Nos. 08782480, which has been allowed but has not been issued, 08954211, 09176741, 09005167. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the claims appear to be drawn to the same J chains and biological agents.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that this application is a member of a family of applications, as indicated in the above double patenting rejections. There are myriad possible provisional statutory, obviousness-type and Schneller-type double patenting rejections which might be made between the claims of the instant application and its various copending applications. It is beyond the resources of the PTO to establish each and every possible double-patenting rejection which might be made among the pending claims. 37 C.F.R. § 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See M.P.E.P. § 822.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Creighton (U_{11}) teaches the peptide bond (page 2, Figure 1-4). Brandztaeg (BG,

cited by Applicants) teaches that sIgM is subjected to rapid degradation in the intestinal juice (page 108, full paragraph 1).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Romeo

DAVID ROMEO
PATENT EXAMINER
February 27, 2000